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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/905,508	08/04/97	SHAYESTEH L	023070-06772

HM12/0330

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EXAMINER	
ARTHUR, L	
ART UNIT	**PAPER NUMBER**
1655	17

DATE MAILED: 03/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/905,508	Shayesteh et al.
Examiner	**Group Art Unit**
Lisa Athur	1655

X Responsive to communication(s) filed on *Dec 19, 2000*

X This action is **FINAL.**

Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

X Claim(s) *37-40* is/are pending in the applicat

Of the above, claim(s) *40* is/are withdrawn from consideration

Claim(s) _____ is/are allowed.

X Claim(s) *37-39* is/are rejected.

☐ Claim(s) _____ is/are objected to.

X Claims *37-40* are subject to restriction or election requirement.

Application Papers

See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

The drawing(s) filed on _____ is/are objected to by the Examiner.

The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

The specification is objected to by the Examiner.

The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

Notice of References Cited, PTO-892

X Information Disclosure Statement(s), PTO-1449, Paper No(s). *11*

Interview Summary, PTO-413

Notice of Draftsperson's Patent Drawing Review, PTO-948

Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. This action is in response to the paper filed December 19, 2000. Claim 36 has been canceled and claim 40 has been newly added. Currently, claims 37-40 are pending. Claim 40 is withdrawn as being directed to a non-elected claim. All of the amendments and arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. Any rejections which have not been reiterated have been withdrawn. This action is FINAL.

2. Newly submitted claim 40 is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claim 40 is drawn to a method of screening for compounds that inhibit the activity of PIK3CA in an ovarian cell while the pending claims are drawn to an in vivo method of inhibiting cellular proliferation in a patient by administration of a PI kinase inhibitor. These methods are patentably distinct because they have different objectives, different method parameters and use different reagents. The screening method is an in vitro method that identifies PI kinase inhibitors that also inhibit cellular proliferation in a cell line while the method of claim 37-39 is an in vivo method for inhibiting cell growth in ovarian cancer cells, i.e. Ovarian tumors, in a patient by administration of a PI kinase inhibitor. The ability of a compound to inhibit cell proliferation in vivo is unpredictable from its activity in vitro is therefore patentably distinct over one another.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the

merits. Accordingly, claim 40 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

MAINTAINED REJECTIONS

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 37 and 38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The essential feature of the claimed invention is the correlation between inhibition of PI kinase activity in cells and the resulting inhibition of proliferation of ovarian cancer cells in patients by administration of an inhibitor of PI kinase activity which more specifically is a non-peptidic inhibitor such as LY294002. The specification teaches that increased PI-kinase activity might contribute to tumor progression by increasing the rate of cell proliferation and tested this hypothesis by incubating cells from an ovarian cancer cell line with the known PI-kinase inhibitor LY294002. The specification teaches that this assay resulted in a significant decrease in cellular proliferation as measured by thymidine incorporation. This decreased proliferation rate was not

observed in cells which had normal PIK3CA copy number. The specification states that these studies suggest that therapeutic agents targeting the PI3-kinase pathway may be effective against ovarian cancers. However, the specification does not describe compounds other than LY294002 which inhibit PI-kinase activity such that a common structural feature of a PI-kinase inhibitory compounds was evident to the skilled artisan from the specification. The claims broadly encompass a potentially large genus of compounds which could inhibit PI-kinase activity, but the specification only describes one specific non-peptidic compound and fails to describe any of the structural feature of this compound which are responsible for its function in inhibiting PI-kinase to result in a decrease in cell proliferation of ovarian cells. The specification contains no description of how LY294002 interacts with Pi-kinase to inhibit its activity, such that the skilled artisan would know what other compounds having similar structure and/or function would be. The compounds which are encompassed by this genus of PI-kinase inhibitors appears to be diverse . Minaguchi et al. (CANCER RES. (1999)59:6063-6067) teach that the PTEN gene product encodes a phosphatidylinositol phosphatase which antagonizes the PI-kinase mediated pathway and suggests that overexpression of this gene product could be effective as a therapy for ovarian cancer by inhibiting PI-kinase activity. This inhibitor is structurally very different from that of LY294002 and the specification clearly did not describe such an inhibitor of PI-kinase. However, the inhibitor of Minaguchi et al. would be encompassed by the claims as written. Consequently, absent a written description disclosing a representative number of species of the PI-kinase inhibitors which function to decrease cell proliferation of ovarian cells, the specification fails to

show that applicant was in fact, "in possession of the claimed invention" at the time the application was filed.

Response to Arguments

The response traverses the rejection on the following grounds. The response argues that applicant is not required to disclose a large number of PI kinase inhibitors that decrease proliferation of ovarian cancer cells and is not required to provide structure-function/activity relationships to satisfy the description requirement. The response instead asserts that applicant is only required to describe [the invention] in sufficient detail to allow the skilled artisan to reasonably conclude that the inventor was in possession of the claimed invention. The response asserts that the specification teaches a correlation between the inhibition of PI-kinase activity with decreased pathological proliferation of ovarian cancer cells. The response then points to the specification as describing a number of PI kinase inhibitors, examples of assays to detect inhibitors of PI kinase activity, assays to assess cellular proliferation and viability of ovarian cancer cells that have been treated with PI kinase inhibitors, and administration of such compounds. The response then concludes that the specification has sufficiently described the claimed invention.

All of the arguments have been thoroughly reviewed but are deemed non-persuasive for the following reasons. This rejection is applied to the methods of claims 37 and 38 because these claims are broadly drawn to the use of a large number of possible compounds to inhibit proliferation of ovarian cancer cells in a patient while the specification has only provided data that one very specific compound, i.e. LY294002, decreased cellular proliferation of cells in an ovarian

cell line *in vitro*. There is no argument that applicant is not required to provide a "large" number of inhibitors that decrease proliferation of ovarian cancer cells and is not required to provide examples of structure-function/activity relationships. However, as pointed out in the response, applicant is required to sufficiently describe the claimed invention such that the skilled artisan would reasonably determine that applicant had possession of the claimed invention at the time of filing. One way to establish that applicant was in possession of the broadly claimed invention is to provide evidence of a number of representative compounds which have the claimed activity, i.e. inhibit cellular proliferation of ovarian cancer cells. Another way to establish that applicant was in possession of a method of using any compound known to inhibit PI kinase activity is to describe a structure-function relationship between the other compounds for which specific data is not presented and the compounds for which the claimed activity was described, i.e. LY294002. As previously pointed out, the art teaches that the PTEN gene product which was not known to be an inhibitor of PI-Kinase activity at the time of filing, I, in fact, an inhibitor of PI-kinase activity. The art suggests that this protein may effect ovarian cancer cell proliferation but does not conclude that it does inhibit proliferation. The specification does not describe PTEN as a compound for use in the claimed method but the claims broadly encompass methods using this compounds. The argument that the specification teaches other PI kinase inhibitors is not support for the claimed method of inhibiting proliferation of ovarian cancer cells by administration of these compounds because the specification has not described the ability of any other PI kinase inhibitors to inhibit cancer cell proliferation in vivo or in vitro. The specification has not established that the

ability of a compound to inhibit PI kinase activity in vitro can be extrapolated to the ability of these compounds to inhibit ovarian cancer in vivo. Consequently, the description in the specification directed to identifying PI kinase inhibitors, assays to assess cellular proliferation and viability of ovarian cancer cells that have been treated with PI kinase inhibitors, and administration of such compounds is not support for the claimed invention because none of these teachings make the connection between the ability of a compound to inhibit PI kinase and the inhibition of PI kinase resulting in the inhibition of ovarian cancer cell proliferation in a patient. Therefore, for all of these reasons, the rejection is maintained.

5. Claims 36-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not provide sufficient guidance and working examples to enable the skilled artisan to make and use the claimed method of inhibiting the pathological proliferation of ovarian cancer cells in a patient by inhibiting PI kinase activity in cells without undue experimentation. The specification teaches that increased PI-kinase activity might contribute to tumor progression by increasing the rate of cell proliferation and tested this hypothesis by incubating cells from an ovarian cancer cell line with the known PI-kinase inhibitor LY294002. The specification teaches that this assay resulted in a significant decrease in cellular proliferation

as measured by thymidine incorporation. This decreased proliferation rate was not observed in cells which had normal PIK3CA copy number. The specification states that these studies suggest that therapeutic agents targeting the PI3-kinase pathway may be effective against ovarian cancers. However, the specification does not describe compounds other than LY294002 which inhibit PI-kinase activity, the specification provide any demonstration that the ability of LY294002 to decrease cell proliferation of an ovarian cancer cell line could be translated to the in vivo environment in a patient. The specification provides no teaching that the in vitro results were known in the art to be predictable when extrapolated into the in vivo environment. Instead the specification states that therapeutic agents which target PI-kinase activity may be effective against ovarian cancer. Shayesteh et al. (Nature Genetics (Jan 1999) 21(1): 99-102.) teach that inhibitors of PI3-kinase will become interesting possible therapeutic agents against ovarian cancer when and if the model that increased PIK3CA copy number and the resulting increase in PI3-kinase activity increase cell proliferation and inhibit apoptosis to allow cells to survive and to genetically evolve into a more malignant phenotype, and if further studies show that PI3-kinase is activated in ovarian tumors as it seems to be in ovarian cancer cell lines. These teachings establish that extensive additional research is still required to determine whether or not inhibition of PI-kinase is a mechanism that will have an effect on cell proliferation in a patient and that the outcome is unpredictable due to the complexity of the mechanisms involved in cancers such as ovarian cancer and the difficulty in extrapolating in vitro results to the in vivo environment. Consequently, for

the reasons set forth above, the skilled artisan would be required to practice undue experimentation to make and use the claimed treatment method.

Response to arguments

The response traverses the rejection on the following grounds. The response argues that the specification has provided sufficient teachings and examples to enable the claimed method by teaching a number of PI kinase inhibitors, examples of assays to detect inhibitors of PI kinase activity, assays to assess cellular proliferation and viability of ovarian cancer cells that have been treated with PI kinase inhibitors, and administration of such compounds. The response asserts that the specification has taught routine assays for use in making the claimed method.

All of the arguments have been thoroughly reviewed but are deemed non-persuasive for the following reasons. The specification has provided guidance as to how the skilled artisan could identify compounds that inhibit PI kinase activity, how compounds which inhibit cellular proliferation in cell cultures can be identified and how to administer a compound to a patient, but the specification provides no guidance as to which of the compounds that inhibit PI kinase activity in vitro will then inhibit cellular proliferation of ovarian cancer cells in a patient. That is the specification has not provided sufficient guidance to enable the skilled artisan to reasonably predict which compounds will in fact be able to inhibit cellular proliferation in patients with ovarian cancer without performing extensive additional research. The specification has only provided evidence that a single compound was able to inhibit cellular proliferation in ovarian cancer cells in vitro. However, the claims are broadly drawn to a method for inhibiting cellular

proliferation of ovarian cancer cells in vivo. In order to enable the claimed invention, the skilled artisan would have to assume that since LY294002 inhibited PI kinase activity and decreased cellular proliferation of an ovarian cancer cell line, then this compounds would also decrease cellular proliferation in ovarian cancer cells in ovarian tumors in a patient and then any compound which was shown to inhibit PI kinase activity necessarily inhibits cellular proliferation in vitro which can necessarily be extrapolated to in vivo activity of this compound. Those of skill in the art do not make these assumptions without extensive experimentation because of the high degree of unpredictability in extrapolating the activity of a compound in vitro to its activity in vivo. Furthermore, as previously discussed, showing that one specific compound which inhibits PI kinase activity has decreases cellular proliferation in vitro is not evidence that all compounds which inhibit PI kinase activity also decrease cellular proliferation. The art has not yet established that increase in PI kinase activity occurs as a result of the increase in copy number of the 3q26.3 region in number of ovarian cancer patients and that this increase in PI kinase activity is the cause of ovarian cancer in these patients. Other genes are contained in the amplified 3q26.3 patients which may be the causative agents in the ovarian cancer in these patients. Also, amplification of 3q26.3 region is not the only associated genetic anomaly association with ovarian cancer, and inhibition of PI kinase in these patients would have an even less likely effect on cell proliferation. As a result of this lack of evidence of association between PI kinase and ovarian cancer, the unpredictability of the claimed method is extremely high thus requiring a very high amount of

further experimentation for the skilled artisan to practice the claimed method. Therefore, this rejection is maintained.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa Arthur whose telephone number is (703) 308-3988. The examiner can normally be reached on Monday- Thursday from 9:30 am to 2:30 pm

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1096.

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600

March 29, 2001